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BREAST

DCE-MRI of the breast in a stand-alone setting outside a complementary strategy - results of the TK-study

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Abstract
Objectives To evaluate the accuracy of MRI of the breast (DCE-MRI) in a stand-alone setting with extended indications.
Materials and methods According to the inclusion criteria, breast specialists were invited to refer patients to our institution for DCE-MRI. Depending on the MR findings, patients received either a follow-up or biopsy. Between 04/2006 and 12/2011 a consecutive total of 1,488 women were prospectively examined.
Results Of 1,488 included patients, 393 patients were lost to follow-up, 1,095 patients were evaluated. 124 patients were diagnosed with malignancy by DCE-MRI (76 TP, 48 FP, 971 TN, 0 FN cases). Positive cases were confirmed by histology, negative cases by MR follow-ups or patient questionnaires over the next 5 years in 1,737 cases (sensitivity 100 %; specificity 95.2 %; PPV 61.3 %; NPV 100 %; accuracy 95.5 %). For invasive cancers only (DCIS excluded), the results were 63 TP; 27 FP; 971 TP and 0 FN (sensitivity 100 %; specificity 97.2 %; PPV 70 %; NPV 100 %; accuracy 97.5 %).
Conclusion The DCE-MRI indications tested imply that negative results in DCE-MRI reliably exclude cancer. The results were achieved in a stand-alone setting (single modality diagnosis). However, these results are strongly dependent on reader experience and adequate technical standards as prerequisites for optimal diagnoses.
Key Points
- *DCE-MRI of the breast has a high accuracy in finding breast cancer.*
- *The set of indications for DCE-MRI of the breast is still very limited.*
- *DCE-MRI can achieve a high accuracy in a 'screening-like' setting.*
- *Accuracy of breast DCE-MRI is strongly dependent on technique and reader experience.*
- *A negative DCE-MRI effectively excludes cancer.*

Keywords DCE-MRI of the breast · Breast cancer · Stand-alone setting · Extended indications · Imaging

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Introduction

Diagnostic breast imaging often supersedes conventional imaging techniques, such as X-ray mammography (XM) and ultrasound (US). Especially in complex cases (young women, cases of reduced visibility, family history of cancer, etc.) second-look ultrasound, tomosynthesis and more frequently DCE-MRI are being conducted simultaneously in order to retrieve diagnostic information and increase diagnostic accuracy.

DCE-MRI is generally accepted to have a very high sensitivity in invasive tumours, due to its ability to detect tumour

angiogenesis as a tumour-specific feature. Tumour angiogenesis is a nutritious necessity for all invasive cancers as soon as the size exceeds 2 mm [1].

Nevertheless, there has been a broad scientific discussion in the past about the specificity of DCE-MRI and its screening capabilities, i.e. to stand alone in the diagnostic setting of today's widespread multimodality approach in breast imaging.

DCE-MRI has been proven to be more accurate than XM plus US, especially in dense breasts [2], yet it is still generally assumed to be a highly sensitive but not very specific imaging technique. DCE-MRI is therefore recommended in the guidelines of ACR only in cases after cancer surgery, status after radiation, status of 'cancer of unknown primary' (CUP), i.e. lymph node metastasis in the axillary region with 'normal' findings in XM and US, cases of very high-risk patients of more than 20–25 % risk of getting breast cancer and breast cancer staging [3]. Other international breast societies, such as the European Society of Breast Imaging (EUSOBI) and European Society of Breast Cancer Specialists (EUSOMA), although slightly more progressive, also still resort to a more or less very limited set of indications [4, 5].

So far the indication 'dense breasts', i.e. ACR breast density categories 3 and 4 [6] where the sensitivity of mammography has been described as rather low (approx. 50 %) [7, 8], has not been listed as a recommended indication for DCE-MRI, although some studies have suggested, that more cancers can be detected using DCE-MRI and that there is no significant correlation between mammographic density and background enhancement in DCE-MRI [9]. A meta-analysis described 16 % change in surgical treatment based on MR findings, varying from 11–24 % [10], and it is also known that the application of DCE-MRI achieves 3–5 % cancer detection in the contralateral breast [11].

In addition, further morphological and kinetic signs have been published, which have helped to increase the specificity of DCE-MRI, i.e. to decrease the number of false positives [12]. Screening studies with high-risk patients indicate that the specificity is really by far not as low as has been described years ago [13]. In Germany there is an ongoing discussion about the role of DCE-MRI in 'complex cases', especially since insurance companies will normally reimburse DCE-MRI in only very few indications, mainly to prevent overdiagnoses. To date, DCE-MRI is therefore embedded in a multimodal approach in most breast centres in Germany.

This study was designed to test the accuracy of DCE-MRI of the breast in our University Hospital in a stand-alone setting, i.e. outside a multimodal diagnostic approach.

Through panel discussions between one of the major German insurance companies and the administration of our University Hospital a new set of indications for DCE-MRI was negotiated and tested.

In addition to the previously existing indications for DCE-MRI, breast specialists from all over Germany were able to refer members of this particular insurance company for DCE-MRI in our hospital. All patients received an MR examination of the breast independent of their previous findings in other modalities. Depending on the MR-findings *only*, patients would either be referred for an MR follow-up or biopsy. This report describes our results from the first 5 years, in which patients were examined by DCE-MRI only. All the patients were controlled by either histology and/or follow-up studies. The question to be answered was what overall accuracy can be achieved using DCE-MRI with the above-mentioned indications in a stand-alone setting?

The complete set of indications for DCE-MRI in this study was:

- Status after breast conserving therapy due to breast cancer
- CUP-syndrome
- Genetic predisposition
- 'Dense breasts' or unclear findings in XM and/or US.

Materials and methods

Patients

All patients gave their written informed consent for the examination in this Institutional Review Board-approved study. The study was HIPAA compliant.

Information about the study indications for DCE-MRI was sent out to breast specialists and patients by mail and was accessible on the website of the insurance company. In unclear cases the referring physicians could receive information through a dedicated hotline operated by the insurance company. Patients travelled at their own expense to our hospital. The insurance company only paid for the DCE-MRI examination (418.50 €).

The study population was a consecutive series of participants (Fig. 1). 1,492 patients were recruited based on the above-mentioned indications. Four examinations could not be completed due to claustrophobia or severe motion artefacts, resulting in 1,488 included patients after the dropouts.

Of the 1,488 patients, 1,226 were examined because they were referred according to 'new indications' as explained above. 266 patients were examined under a 'conventional indication' as suggested by the ACR [3]. A detailed list of indications for referral with their ICD 10 (International Statistical Classification of Diseases and Related Health Problems) subgroups is shown in Figs. 2 and 3 [14].

The mean patient age was 53.6 years. 156 patients had undergone previous surgery or previous chemotherapy after cancer more than 1 year prior to the examination. The time interval between the DCE-MRI examination of the breast and a follow-up biopsy or surgery was less than 3 months. There

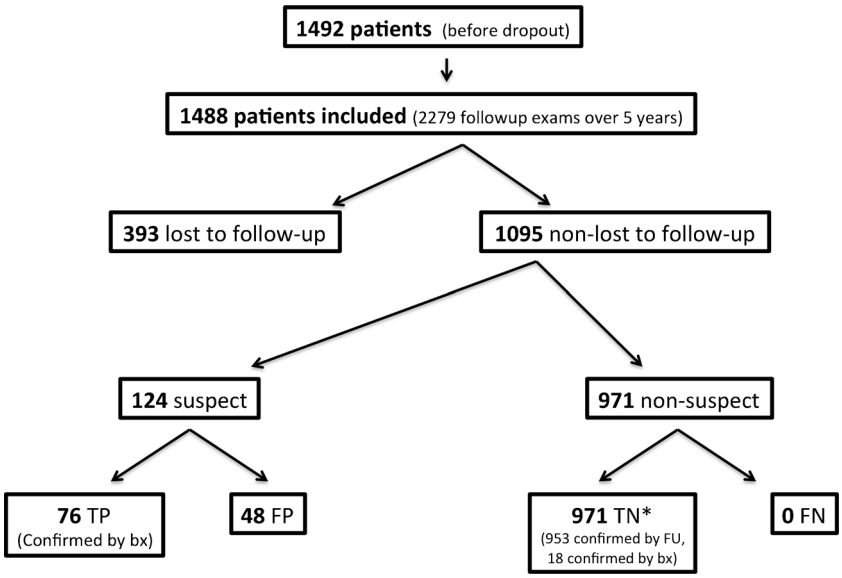

Fig. 1 Patient collective of our study (*: 18 patients received biopsy upon external request, despite negative MR-findings)

was no other treatment between the DCE-MRI examination and biopsy.

The reference standard was the follow-up histological evaluation after biopsy, surgical treatment or a follow-up examination over the following 2–4.5 years. Histopathological evaluation after biopsy was performed in various hospitals throughout the country. 18 patients received a biopsy, despite a negative test result in the DCE-MRI examination, due to the recommendation of referring physicians, insisting on histological correlation (Fig. 4).

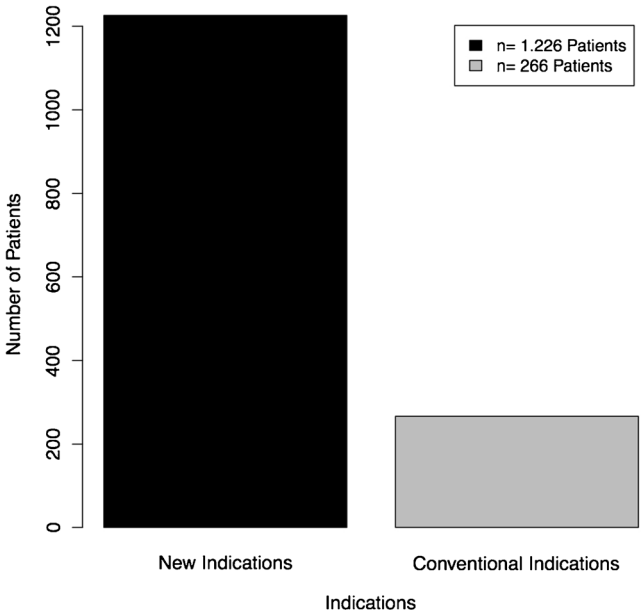

Fig. 2 'Conventional' and 'new' indications for DCE-MRI of the breast in patients referred to our University Hospital by physicians, gynaecologists and radiologists from throughout the country

Upon a positive finding in DCE-MRI, the description of the tumour size and exact location was included in our medical report. DCE-MRI-reports were sent by fax or mail within 2 days.

A total amount of 2,272 DCE-MRI examinations (including the follow-up examination) was performed over the period of 69 months (01/04/2006 until 31/12/2011). 761 patients were examined in a follow-up of more than 2 years. Initial examinations were finished in December 2009 in order to receive the result of at least one 2-year follow-up examination in December 2011. 151 patients were followed-up more than once. The examinations were performed within a prospective study, i.e. the data collection was planned before the reference standard histology or follow-up were performed (Fig. 4).

Test methods

Patients in whom DCE-MRI indicated cancer or DCIS were histologically correlated in a follow-up histological evaluation, either by biopsy and/or by surgical excision. The MR examination was performed as shown in Table 1.

Preparation

Before a planned DCE-MRI examination extensive patient education about risks, the examination itself and contraindications was conducted, including patient anamnesis (i.e. day of the menstrual cycle, and breastfeeding, tumour, hormone and family history). Patients taking hormone replacement therapy (HRT) were asked to stop the HRT 4 weeks prior the DCE-MRI examination. Directly before being put into the scanner, the patients were asked to minimize motion in order to prevent artefacts.

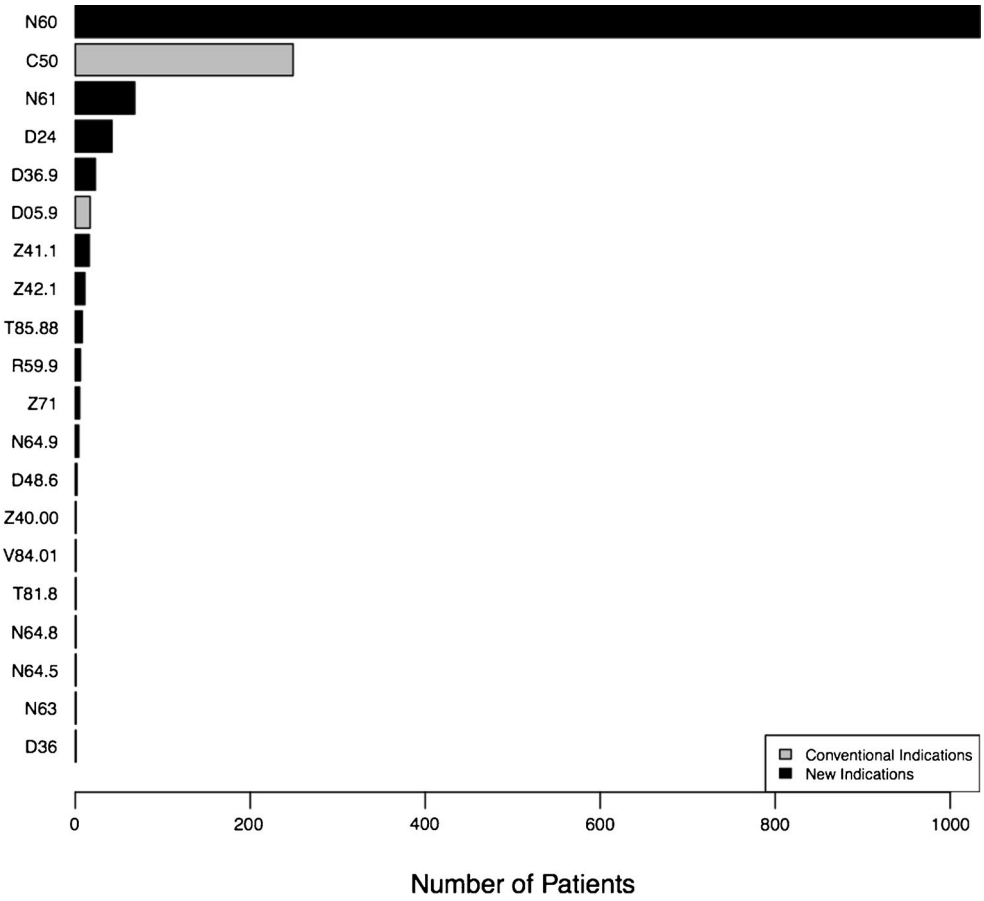

Fig. 3 Subgroup analysis of 'conventional' and 'new' indications for DCE-MRI of the breast in patients referred to our University Hospital by physicians, gynaecologists and radiologists from throughout the country for this study

Referring physicians

Referring doctors were mostly gynaecologists, and all were board-certified, who are responsible for all aspects of women's imaging in Germany, i.e. pelvic *as well as* breast disease. The referring physicians were informed (by flyer and/or telephone and/or website) by the insurance company about the study intentions and the opportunity to send patients to our hospital for paid DCE-MRI. These referring doctors work in hospitals or private practices all over Germany. The patients paid for the travel expenses to our hospital (a trip of between a few up to 500 miles depending on the distance to our facility).

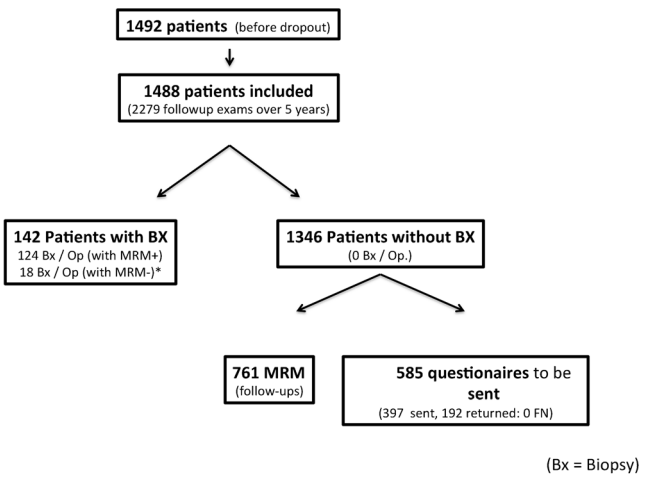

Fig. 4 Biopsies performed in our patient collective (*: 18 patients received biopsy upon external request, despite negative MR-findings)

Image acquisition and interpretation

All DCE-MRI examinations were performed with a 1.5 Tesla-MR Scanner (Siemens Symphony and Avanto) using the following protocol, which is also described in detail in other publications (Table 1) [15].

The DCE-MRI examinations were performed and diagnosed by *one* experienced radiologist (>29 years of experience in DCE-MRI). Directly after the MR exam, the result was communicated to the patient and the referring gynaecologist/surgeon by fax or mail. In case of a 'non-malignant MR diagnosis' (1,364 pats), patients were subject to continuous 2-year follow-ups by DCE-MRI or inquiries by mail about their health status and treatments they had received.

Table 1 Examination protocol

Sequence (No.)	1. Nat cor	2. Dynamic* tra	3. CM cor	4. T2-TSE	5. STIR
Weighting	T1	T1	T1	T2	T2 (T1, 150 ms)
Pulse sequence	FLASH	FLASH	FLASH	TSE	TSE
Orientation	cor	transv	cor	transv	transv
TR (ms)	113	113	113	8900	8420
TE (ms)	4.6	4.6	4.6	207	70
Flip angle (°)	80	80	80	191	180
Slice thickness (mm)	3	3	3	3	3
Gap (mm)	0	0	0	0	0
Field of view (mm)	350	350	350	350	350
No. of slices	44	44	44	44	44
Matrix (pixels)	230×256	307×384	230×256	435×512	326×384

* Connotation: dynamic study before and after the intravenous application of 0.1 mmol Gd-DTPA per kg body weight within 10 s, followed by the injection of 30 ml saline via an automatic injector (Medrad, Spectris, Pittsburgh) with 3 ml/s

Statistical methods

Diagnostic parameters were calculated using the following formulas:

Sensitivity: TP/(TP + FN); specificity: TN/(TN + FP); positive predictive value (PPV): TP/(TP + FP); negative predictive value (NPV): TN/(TN + FN); accuracy: (TP + TN)/(TP + FP + FN + TN); positive likelihood ratio: sensitivity/1-specificity; negative likelihood ratio: 1- sensitivity/specificity.

Results

Among 1,488 included patients, 142 were sent for biopsy, 124 due to suspicious DCE-MRI results, and 18 because of the recommendation of external physicians despite a negative, i.e. non-malignant, MR result (Fig. 4). 971 patients had non-malignant results in DCE-MRI. In these patients no further examination aside from follow-up examinations over the next 2–4.5 years was performed as advised in the study agreement. 761 DCE-MRI control examinations confirmed the first DCE-MRI results. 585 letters of inquiry were sent out to the patients not participating in follow-up examinations. Within the study's time limits, 192 questionnaires were returned with no report of a false negative case, i.e. no patient with cancer was detected in the group of patients, where DCE-MRI did not indicate cancer. 393 patients were lost to follow-up or did not answer the questionnaires within the study's time limits. Table 2 lists our results concerning the DCE-MRI diagnosis versus histology and follow-ups.

Cancer was diagnosed in 90 patients with DCE-MRI with correlating histological results revealing cancer in 63 cases, whereas in 27 cases no cancer could histologically be found. DCIS was diagnosed in 34 patients – histology results revealed 13 cases of DCIS and 21 non-malignant results.

We have no evidence of false negative cases. This included 18 patients with a benign biopsy and 1,737 examinations, in which the follow-up or inquiry was negative (Table 2). In total 76 cases of cancer had been found and confirmed in this study. 48 cases were described as false positives leading to a sensitivity of 100 %, specificity of 95.2 %, PPV of 61.3 %, NPV of 100 % and an accuracy of 95.6 % (Table 3).

In these results the diagnoses of both cancer and DCIS were considered malignant. A specific analysis for invasive cancers only resulted in a sensitivity of 100 %, specificity of 97.2 %, PPV of 70 %, NPV of 100 % and an accuracy of 97.5 % (Table 4).

Discussion

The results of our study show that DCE-MRI is able to achieve a high sensitivity as well as a high specificity in a stand-alone setting with extended indications as well as a

Table 2 Results of MR diagnosis vs. histological correlation and follow-ups

DCE-MRI – diagnoses		Histology		Follow-up		Lost*
(1,488 patients)		CA / DCIS	Benign	Malignant	Benign	
Cancer	90	63	27	0	0	0
DCIS	34	13	21	0	0	0
Benign	2148	0	18	0	1737	393
Total	2272	76	66	0	1737	393

*No questionnaire received within the study's time limits

Table 3 Sensitivity, specificity, NPV, PPV and accuracy of MRM in our University Hospital

	Patients	Results
Sensitivity	76 / 76	100 % (95 % CI: 95.19–100 %)
Specificity	917 / 1019	95.2 % (95 % CI: 93.8–96.4 %)
PPV	76 / 124	61.30 %
NPV	971 / 971	100 %
Accuracy	1047 / 1095	95.60 %
Pos. Likelihood Rat.	100 / (1 – 0.952)	20.83
Neg. Likelihood Rat.	(1 – 1) / 95.2	0

heterogeneous population of referring physicians. The heterogeneity of the collective of referring physicians can be discussed as a negative hallmark of this study. However, it reflects a representative image of the everyday clinical routine in which DCE-MRI in a stand-alone setting was supposed to be tested.

Our study was to our knowledge the first to consecutively introduce this new set of indications for DCE-MRI into clinical routine in order to test for outcome in a stand-alone setting.

The results of MR-only-based diagnoses in our study population of 1,488 patients resulted in 142 necessary biopsies and 76 necessary excisions of small cancers. However, the majority of patients (971 patients) did not require any further diagnostic, surgical or medical treatment, which was confirmed in MR-controlled follow-up studies or inquiries by mail.

It is important to mention that the indication for the MR mammogram was not determined by our department (the examiner), but by external referring gynaecologists or surgeons and the results validated by histology and/or follow-up (see Figs. 1 and 4).

It can be estimated that all 76 histological proven cancers were small stage I cancers, i.e. below 2 cm in size, resulting in a relatively uncomplicated and not very extensive breast conserving operation. We assume that the monetary and psychological aspects as well as the overall time-in-hospital caused by such a 'limited' operation were significantly lower than they would have been had DCE-MRI not been performed. These cancers would have most likely been detected years later at a size and stage in which diagnostic and medical efforts in treatment would have been severely higher.

Table 4 Results concerning invasive malignant lesions only

	Patients	Results
Sensitivity	63 / 63	100 % (95 % CI: 94.25–100 %)
Specificity	971 / 998	97.20 % (95 % CI: 96.1–98.1 %)
PPV	63 / 90	70 %
NPV	971 / 971	100 %
Accuracy	1034 / 1061	97.50 %

We assume that most of the patients in this study will most likely not die of breast cancer, as the prognosis of breast cancer in this stage is known to be favourable, according to mammographic screening studies: with a size of less than 2 cm at the time of diagnosis the 20-year survival rate has been shown to be above 95 % [16].

A critical argument could be the inclusion criteria for the study: Approximately 1,500 external colleagues referred patients for DCE-MRI to our University Hospital. This resulted in a heterogeneous array of physicians responsible for providing the indication for DCE-MRI. However, it is exactly the type of setting that a 'screening scenario' conducted with MR would resemble.

The exact evaluation of indications for DCE-MRI among nearly 1,500 referring physicians was in fact not the subject of this study. However, this study was able to show that a high sensitivity (100 %) as well as a high specificity (>95 %) can be maintained, independent of the reason for referral or the referring physician.

Mammographic as well as sonographic details, such as what percentage of patients had lesions with irregular margins, architectural distortions, microcalcifications or suspicious US findings, were not considered for the final diagnosis. The purpose of this study was solely to evaluate the outcome for the new set of indications for DCE-MRI in a stand-alone setting, as agreed upon when designing the study with the insurance company compensating for the MR examinations.

DCE-MRI is challenging in technique and diagnosis and has a long learning curve. Both - high sensitivity and high specificity through many years of experience and constant evaluation of morphological and kinetic signs are essential prerequisites for the results of this study. Even though this study was intentionally designed as a mono-reader study as an explicit condition for the insurance company to participate, it would be interesting to evaluate intra-observer variability as well as reproducibility in a multicentre setting. Future research will be able to address this issue.

Interestingly, no false-negative cases were recorded within the study's time limits, strongly indicating that a negative MR does effectively exclude cancer, which is in line with several other studies [17, 18]. The reason might be the unique ability of DCE-MRI to detect the one tumour-specific sign of

malignant lesions, i.e. tumour-angiogenesis. However, a non-diagnosis of low-grade DCIS cases, which might not yet have induced tumour-angiogenesis, is possible and will probably only be detected through lengthy follow-ups. In addition, these low-grade DCIS lesions are questionable in their real malignant potential and prognosis; the WHO no longer describes them as 'cancers' but as DIN (ductal intraepithelial neoplasia) lesions in an attempt to avoid over- diagnosis and treatment [19]. However, the prognostic impacts of these changes are still to be clarified in the future.

Our results may not only represent a step towards a general acceptance of DCE-MRI, but also a suggestion of the future extension of the list of DCE-MRI indications as suggested by the EUSOBI [4]. Some studies [20, 21] already indicate that additional diagnostic examination with US or XM does not result in any valuable additional medical information if DCE-MRI is used. However, our results have to be validated in future multicentre studies, using different DCE-MRI techniques, which are most probably different in their diagnostic accuracy.

If the results of this study can be confirmed within an even larger patient collective after a consensus on the level of training of the examiner, the choice of examination technique and the use of important signs for the evaluation of the images – DCE-MRI of the breast may not only become the relevant diagnostic tool for the evaluation of breast lesions but also the screening tool for all women. Expertise, however, requires a broader acceptance of DCE-MRI of the breast.

There are several studies addressing the topic of adjusting DCE-MRI in length to cut on scan-related costs in order to make MRM eligible for screening [22, 23, 17].

Although we believe that DCE-MRI should be optimized to achieve an optimal accuracy to make it fit for screening, we estimate a different factor to be far more important: By improving reader experience and achieving a standardization of technique on a broad scale through teaching and training, the financial efficacy of DCI-MRI is optimized rather by spending time on maximizing accuracy than by saving on scan time. Breast screening with MR might be feasible if we considered the saved costs through the prevention of unnecessary biopsies, reduced surgical scales of tumours found at an earlier stage and adaption of radio chemotherapy through the application of optimal DCR MRI of the breast, i.e. optimal reader experience paired with optimal technique.

We know currently that we are not necessarily able to increase the accuracy of DCE-MRI of the breast by alterations in field strength and technique [24–27] above levels achieved in this study with simple sequences run on a 1.5 tesla magnet. However, we have found that it is possible to reach accuracy levels above 88 % at an NPV level of 100 %, using simple decision trees [18] of only five selected diagnostic criteria. Somewhere along that line we have to find out whether the reduction in scan time, finding the optimal technique or a mixture of the two will have the greatest impact on the feasibility of breast MR in a screening population.

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